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Hepatitis C virus treatment revolution: need for close monitoring

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Hepatitis C virus (HCV) infection is a relevant clinical and public health problem. The virus infects approximately 3% of the global population, and is one of the leading causes of end-stage liver diseases and hepatocellular carcinoma, causing >350 000 deaths yearly [1].

Unlike from other agents causing chronic infections (e.g. human immunodeficiency virus and hepatitis B virus), HCV cannot establish a permanent intracellular genomic archive, and its persistence relies on continuous replication. Hence, HCV can, theoretically, be eradicated from the host, provided that new replication cycles are prevented [2].

For >20 years, the combination of pegylated interferon (Peg-IFN) and ribavirin was the pillar of anti-HCV therapy, often being referred to as the standard of care (SOC). However, the success rate of the SOC is only approximately 50% overall. Furthermore, patients in whom there is a failure to clear HCV with SOC have little (if any) chance of subsequent treatment with the same combination being successful, and, perhaps more importantly, patients with comorbidities are ineligible to receive Peg-IFN at all [2].

Recently, compounds with direct antiviral activity (DAAs) have been discovered. The first-generation protease inhibitors (PIs) telaprevir and boceprevir were approved by the FDA on May 2011 for HCV genotype 1 in combination with the SOC. These combinations significantly improved viral clearance, but with a significant increase in adverse events. Moreover, the issue of subjects ineligible to receive Peg-IFN remained unsolved [3,4].

Subsequently, two new drugs, sofosbuvir (NS5B polymerase inhibitor) and simeprevir (second-generation PI), have been approved. Many other compounds, with different viral targets, will enter clinical practice soon, including three NS5A inhibitors (ledipasvir, daclatasvir, and ombitasvir), two-second generation PIs (asunaprevir and ABT-450), and one NS5B inhibitor (dasabuvir). Combinations of these compounds promise all-oral, once-daily, ultra-short (8–12 weeks), interferon-free treatment with outstanding efficacy, an improved safety profile, and no comorbidity contraindications. It is common opinion that, owing to these new options, HCV will not represent a significant health issue in the near future [3–5].

However, this optimism hides several critical issues. Among them are: prohibitive cost of the therapy; the best drug combination(s); when to start treatment and how long to treat; and transmission by asymptomatic carriers.

Furthermore, it is our firm opinion that another topical issue that is not sufficiently addressed by current guidelines is therapeutic response monitoring, which is focused on the measurement of HCV RNA in the blood, and is aimed at optimizing therapy duration, to prompt early discontinuation to prevent potential side effects, and to reduce unnecessary costs.

Currently, it is assumed that the best chance of HCV eradication in a patient occurs when viral replication has been halted for a sufficient time to allow its disappearance from every infected cell. However, even in cases when HCV RNA is not detected with the most sensitive assay, it is still possible that minute, undetected amounts of virus are present. Previous experience with the SOC has indicated that assays with higher sensitivity perform better in predicting sustained virological response in patients who have reached the end of therapy response. In this respect, the diagnostic armamentarium for monitoring HCV therapy has improved greatly, and the sensitivity of current real-time PCR-based assays has substantially improved as compared with the first-generation assays. It is not clear whether the sensitivity of current assays could be further improved, and whether such improvements would offer any advantage in monitoring DAA-based therapy.

There is a general consensus that the rate of decay of HCV RNA is predictive of response. Clear stopping rules have been established for the SOC, to allow treatment duration to be adapted on the basis of early decay of viral load, and even for treatment to be stopped in cases of insufficient or absent decline. However, for the DAA-containing regimens, therapy tailoring indications and stopping rules have been formulated for a very limited number of compounds; in addition, there is a great degree of variability in the cut-off levels to adopt, even for DAAs with similar mechanisms of action and administration schedules. In fact, negative and positive predictive values of different cut-off levels have been established with respect to different endpoints and criteria, so that a uniform decision pathway is lacking [3].

Another highly debated issue in monitoring strategies is resistance to antivirals. Owing to the high replication rate of HCV, and to the lack of proofreading activity of viral polymerase, HCV is highly variable, and each possible mutation, and even each combination of mutations, arises every day within each infected individual, representing the basis for selection of resistant variants by DAAs [6]. Despite reduced

fitness, such variants rapidly overgrow wild-type viruses, often favoured by the accumulation of additional, fitness-restoring, mutations [7]. Actually, natural variants carrying resistance-associated mutations have been widely described in both conventional and next-generation sequencing-based studies, and have been shown to rapidly accumulate throughout the course of DAA treatment, if viral replication is not completely suppressed [8,9]. However, there is no agreement on the usefulness of performing resistance testing prior to the initiation of DAA-based therapy; even the use of resistance testing in failing cases is questioned, for a number of reasons. In fact, not all virological failures are accounted for by the emergence of resistant variants; the resistant variants rapidly decline (although they do not always disappear) after treatment is stopped; and the availability of different classes of drugs, and their combined use, may achieve an enormous increase in the genetic barrier to antiviral resistance, overcoming this problem.

In conclusion, the main firm point is that the new interferon-free combinations will be much more effective and less toxic than previous regimens. However, the upcoming treatment revolution will pose significant clinical challenges. The recent history of HCV therapy was dominated by punctual, well-settled and widely accepted guidelines that provided clinicians with detailed indications on who to treat, and for how long and when. In contrast, in the immediate future, clinicians will face significant uncertainties regarding how to manage their patients. Virologists are requested to face these challenges by establishing/validating suitable markers and predictors to assess viral eradication and provide guidance to clinicians.

Transparency Declaration

The authors declare no conflicts of interest.

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